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Impact of the introduction of high-sensitive troponin assay in the emergency department: a retrospective study

Running head: Introduction of high-sensitive troponin assay in the emergency department

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Key words

Troponin test, high-sensitive troponin test, acute coronary syndrome, overdiagnosis, non-cardiac chest pain, chest pain

Abstract

Background: Compared to troponin T/I test, the introduction of a high-sensitive (hs) troponin test may result in a higher proportion of positive test results in patients with chest pain and over testing in patients without acute coronary syndrome. We assessed the impact of the introduction of the hs-troponin assay on the discharge diagnoses and the number of diagnostic tests in patients presenting with chest pain in a real-life setting in an ED.

Methods: Retrospective chart review of patients presenting with chest pain to one of the largest hospitals in Switzerland. We compared the standard troponin period (12/2009 to 11/2010) to the hs-troponin period (12/2010 to 12/2011).

Results: Data from 1,274 patients (standard 597 (46.9%), hs-troponin 677 (53.1%)) were analyzed. The proportion of patients with NSTEMI increased (hs-troponin 14.9% compared to 9.7%); the proportion in unstable angina (1.5% to 4.0%) and other cardiac illnesses (8.1% to 11.7%) decreased. Although the proportion of non-

cardiac chest pain illnesses (67%) remained unchanged, the proportion of positive hs-troponin was higher (6.1% vs. 2.0%). The average number of additional tests/person decreased in troponin positive patients (2.0 to 1.7 test per patient; p=0.02) and troponin negative patients (3.1 to 2.8 tests; p<0.0001).

Conclusion: Although the introduction of the hs-troponin test resulted in a higher proportion of positive hs-troponin tests in patients with non-cardiac chest pain, the average number of diagnostic tests decreased in patients with chest pain presenting to an ED indicating an increased confidence of clinicians in their diagnosis.

Clinical Significance

- Chest pain accounts for approximately 10% of all ED visits and up to 90% have no underlying cardiovascular disease.
- The introduction of a high-sensitive troponin test may result in downstream testing due to a higher proportion of positive results particularly in patients without cardiac chest pain.
- After the introduction of the hs-troponin test in the real-life ED setting, we observed a decrease in the overall non-invasive and invasive diagnostic testing.

Introduction

The top priority in patients with chest pain attending an emergency department (ED) is to identify a potentially life-threatening disease such as an acute coronary syndrome, pulmonary embolism, or pneumonia. In the USA, chest pain accounts for approximately 10% of all ED visits (1). Acute coronary syndrome is categorized based on symptoms, ECG, and cardiac biomarkers into acute ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (2, 3). Compared to patients with a NSTEMI, patients with unstable angina report a typical chest pain without elevated cardiac biomarkers

(2-4). After a careful diagnostic work-up of patients presenting with chest pain to an ED, 60% to 90% have no underlying cardiovascular disease (5-8).

To date, the most sensitive cardiac biomarkers used to diagnose acute coronary syndrome are troponin T and I. Cardiac ischemia may result in the damage of myocytes and a release of troponin into the blood. To diagnose an acute coronary syndrome earlier, a high-sensitive troponin (hs-troponin) test was introduced into clinical practice. A direct comparison between the hs-troponin and a standard troponin T/I tests showed a higher sensitivity (94% vs. 72%) with a decreased specificity (73% vs. 95%) (9). While the higher sensitivity allows to detect an acute coronary syndrome earlier (10, 11), the decreased specificity may result in more patients with suspected but not confirmed acute coronary syndrome (12). This may thus lead to more tests to rule out cardiac disease. How the introduction of the hs-troponin test affects clinical practice is unknown.

The objective of this retrospective study was to assess the impact of the introduction of the hs-troponin assay in the real life setting on discharge diagnoses and the diagnostic evaluation in patients presenting with chest pain to an ED. We hypothesized that the introduction of the hs-troponin test resulted in a more intensive diagnostic evaluation in patients with a positive hs-troponin test and no acute coronary syndrome to rule out a cardiac disease.

Methods

Single-center, retrospective medical chart review of patients presenting to one of the ten largest hospitals in Switzerland, the cantonal hospital Winterthur (>30'000 ED visits annually), between December 1, 2009 and December 31, 2011. The study period was chosen because on December 1, 2010 a hs-troponin assay was

implemented and in January 2012 an outpatient clinic near the hospital opened and many patients, eligible for this study, were treated elsewhere.

Patient selection

Potentially eligible medical records were identified by using diagnostic ICD-10 codes: R06.4 (hyperventilation), R07.1 (chest pain when breathing), R07.2 (precordial pain), R07.3 (other chest pain), and R07.4 (chest pain not specified), I20 (angina pectoris), I21 (acute MI), I22 (recurrent MI), I23 (complications after acute MI), and I24 (other acute ischemic heart disease).

Eligibility criteria

All medical records of adult patients (≥18 years) presenting to the ED with chest pain of cardiac or non-cardiac diagnosis with ≥1 troponin test.

Excluded were records with no baseline troponin test, pregnancy, trauma patients or life-threatening conditions, malignant disease, current fracture, renal replacement therapy or severe kidney failure (creatinine clearance of less than 30ml/min/1.73m^2), patients with disability or patients disagreeing that their data will be used for scientific purposes.

Study cohort and data extraction

Additional description of the extraction methods have been described elsewhere (13, 14). Two researchers (TD, SM) screened all records for in-/exclusion. Unclear cases were discussed with the principal investigator (PI, MW) and disagreement was resolved by consensus. Each patient included in the study was assigned a unique de-identified number. We defined the first presentation for chest pain to the ED as the index consultation. During the following three months each presentation to the hospital was considered potentially related to the index consultation and extracted as a follow-up consultation. All presentations after >3 months due to chest pain were defined as a new index visit of a second episode.

The extraction form with predefined variables was pilot-tested in 20 records. To ensure high-quality data extraction, TD/SM were trained and monitored by MW/SH and an extraction manual was used. We extracted information on general characteristics (age/gender), cardiovascular risk factors, signs/symptoms at presentation, preexisting comorbidities, medications, clinical findings, blood analyses, ECG, and invasive/non-invasive testing. Further, information on discharge diagnosis, and treatment recommendations were extracted.

One researcher not involved in the extraction process (BK) assessed the data extraction quality by reviewing six predefined parameters (troponin test result, pain reproducible by movement, coronary angiography, recommendation for further diagnostic evaluation, recommendation for further treatment, and the discharge diagnosis) in 379 (26%) ED visits. The overall quality of data extraction was high (error rate 5.4%, 95% confidence interval (CI) 4.5–6.4) and for the troponin values very high (error rate 0.8%, 95%-CI 0.2–2.5).

Study endpoints of interest

We compared the proportion of acute coronary syndrome diagnosis (NSTEMI, STEMI, unstable angina), other cardiac illnesses, and non-cardiac chest pain between the standard troponin test period and the hs-troponin test period. We further compared the number of additional non-invasive cardiac tests (i.e. tread mill tests, myocardial mibi-scintigraphy, and echocardiography (echo)), invasive cardiac tests (i.e. coronary angiography), and non-invasive non-cardiac tests (i.e. chest x-ray, computer tomography (CT) of the chest or abdomen (e.g. to rule out pulmonary embolism), sonography of the abdomen or pleura, lung function tests).

Acute coronary syndrome diagnoses was based on the AHA/ACC definitions (9): (1) STEMI in persistent ST-elevation or anterior ST depression indicative of true posterior MI (i.e. ST-elevation of 0.1mv in ≥2 leads or ≥0,2mV in lead V2 and V3 in

men (aged ≥40J) or ≥0,25mV (age <40J) or ≥0,15mV in women); (2) NSTEMI in changes on ECG (i.e. ST depression, transient ST-elevation, or new T-wave inversion) or normal ECG, and dynamic changes in cardiac biomarkers; (3) unstable angina in typical symptoms for angina pectoris without myocardial ischemic injury (i.e. normal ECG and normal troponin).

All other cardiac disease were assigned to “other cardiac illnesses” (e.g. myocarditis, hypertensive emergency without acute coronary syndrome, Takotsubo myopathy). All diagnoses not related to a cardiac disease were assigned to the non-cardiac chest pain group.

The final diagnosis was based on the diagnosis of the discharge letter or, in patients with follow-up visits / readmissions, adjudicated by a committee not involved in the data extraction (JS, UH, JB, MW) and blinded to the discharge diagnosis of the first letter.

Troponin assay

Standard troponin test period: the third generation troponin T-Assays (CARDIAC T, Ref. 04491815 190, Cobas®, Roche) was used with a limit of detection 0.01ng/ml troponin T and a cut-off of ≥0.01ng/ml (15).

Hs-troponin period: on December 1, 2010, the fourth generation hs-troponin T assay (Troponin T hs STAT assay, Ref. 05092728190 V8, Cobas®, Roche) was implemented with a limit of detection of 0.003ng/ml troponin. The cut-off for pathological hs-troponin values was defined at ≥0.014ng/ml, the 99. percentile of the reference population (coefficient of variation <10% (16)). According to a meta-analysis a cut-off level of ≥0.014ng/ml resulted in a sensitivity of 89.5% (95%-CI 86.3-92.1%) and 77.1% (95%-CI 68.7-83.7%) (17). None of the assay batches known to have calibration errors (batch numbers 157120, 160197, and 163704, produced

between October 2009 and April 2012, with the latest expiration date of October 2012) were used during the study period.

Statistical Analysis

We calculated median and interquartile ranges for continuous variables, absolute numbers and percentages of total for categorical variables. Based on the pre-test probability (prevalence of an illness in the total study population), we calculated the post-test probabilities after a positive / negative standard troponin and hs-troponin tests with or without ST-segment elevation in the ECG. We used Kruskal-Wallis rank sum tests to compare the average number of additional test (ECG, coronary angiography, scintigraphy, Echo, chest x-ray, computer tomography (CT) of the chest or abdomen, sonography of the abdomen or pleura, gastroscopy, lung function tests). We calculated average monthly tests per patient and compared mean tests per patient between groups. We used a t-test to quantify the evidence for differential number of tests per patient in each period. Between-group differences were estimated with 95% confidence intervals. As various factors may influence the number of diagnostic tests, we performed sensitivity analyses for the number of non-invasive / invasive cardiac tests (i.e. treadmill test, coronary angiography, mibi-scintigraphy, and echocardiography) and the number of diagnostic tests after the exclusion of STEMI patients. All analyses were performed with the statistical software R for windows (18). The STROBE guidelines were used for reporting of the study.

Ethical Review Board Approval

Due to the retrospective nature of the study data extraction did not interfere or influence the treatment of patients. The study was approved by the local ethics committee (KEK-ZH number 2014-0506, approved in December 2014) and complied with international standards including the declaration of Helsinki, the Swiss law for research in human subjects, and the Swiss academy for medical science (SAMW).

Results

Out of 22,365 visits to the internal medicine ED 3,000 records were screened and 1,467 records (6.6%) were extracted (**Figure 1**). In 193 (13.2%) ED visits no troponin test was performed, leaving a study population of 1,274 patients (86.8%, 597 in the standard troponin T and 677 in the hs-troponin test period).

Baseline characteristics

The study populations were similar in terms of age (mean age 55 years), body mass index, civil status, referral, smoking, family history of myocardial infarction, gastrointestinal diseases, cocaine use, and co-medication use (**Table 1**). The differences in the baseline characteristics between the two study periods were small: a higher prevalence in the hs-troponin group was found for thyroid disease (5.0% vs. 4.4% in the standard group). A lower prevalence in the hs-troponin group was found e.g. for diabetes (11.2% vs. 12.1%), history of peripheral arterial disease (2.2% vs. 3.4%), stroke (3.0% vs. 4.0%), or myocardial infarction (14.2% vs. 16.4%), psychiatric diseases (12.0% vs. 14.4%), and known cardiovascular disease (48.6% vs. 54.9%).

Proportion of acute coronary syndrome before and after the introduction of the hs-troponin test

We observed during the hs-troponin test period a higher proportion of NSTEMI (14.9% vs. 9.7%) and a lower proportion of unstable angina diagnoses (1.5% vs. 4.0%, **Table 2**). The proportion of other cardiac illnesses was lower (8.1% vs. 11.7%) and remained unchanged for non-cardiac chest pain (67.1 and 67.2%). A positive first troponin test result was more frequently observed in the hs-troponin period

(STEMI 100% vs. 63.6%, NSTEMI 82.2% vs. 65.5%). In patients with non-cardiac chest pain, the hs-troponin test was positive in 6.1% compared to 2.0% in the standard test period. Figure 2 depicts the influence of a positive or negative troponin test result on the posttest probabilities of the respective diseases (standard troponin test period **Panel A;** hs-troponin test period **Panel B**). In patients with a non-cardicac chest pain diagnosis, a negative first troponin test increased the posttest probability by 10% (77 vs. 67%) in the standard troponin period and by 21% in the hs-troponin period (88 vs. 67%).

Diagnostic tests before and after the introduction of the hs-troponin test

The average number of diagnostic tests decreased in patients with a positive troponin test from 2.2 (SD 1.1) to 1.7 (0.8) and in patients with a negative test from 3.2 (0.9) to 2.9 (1.1) per patient in the hs-troponin period (**Figure 3**). Compared to the hs-troponin test period, more additional tests were performed in the standard test period for troponin-positive (Beta 0.28, 0.07 to 0.49; p=0.008) and troponin-negative patients (Beta 0.44, 0.31 to 0.56, p<0.001).

Sensitivity analyses

Results were consistent when restricting the analysis to non-invasive / invasive cardiac tests and after the exclusion of STEMI patients (14).

The monthly average non-invasive / invasive cardiac tests performed per patients was higher in the standard group in troponin positive patients (Beta 0.20; 95% CI 0.04 to 0.35 p=0.012) and also troponin negative patients (Beta 0.16, 95% CI 0.09 to 0.23, p<0.001) compared to the hs troponin test period.

After the exclusion of patients with a STEMI diagnosis, the monthly average additional tests performed per patients was higher in the standard group in troponin

positive patients (Beta 0.35, 95% CI 0.09 to 0.60 p=0.008) and also troponin negative patients (Beta 0.44, 95% CI 0.31 to 0.56, p<0.001) compared to the hs troponin test period.

Discussion

Contrary to our main hypothesis, the introduction of the hs-troponin test in the ED resulted in a decrease in the number of diagnostic tests performed in patients presenting with chest pain to an ED. Not surprising, a higher proportion of NSTEMI and a lower proportion of unstable angina diagnoses was observed. Although more positive hs-troponin test results in patients discharged with non-cardiac chest pain were detected, the proportion of non-cardiac chest pain illnesses remained unchanged. The higher proportion of positive hs-troponin tests did not to translate into a more intensive non-invasive and invasive diagnostic testing.

Results compared to the literature

The introduction of the hs-troponin test prompted a discussion on the overdiagnosis of cardiovascular disease in patients with chest pain (12). Whereas a study showed that lowering the diagnostic threshold for detecting blood troponin identified more patients at risk for recurrent myocardial infarction (19), other studies found no overall impact on risk of myocardial infarction or cardiovascular death (20, 21). In a study in 48,282 patients with suspected acute coronary syndrome the introduction of the high-sensitivity troponin test resulted in a reclassification of 17% to myocardial injury (20). Only in one third this was due to a myocardial infarction as a result of coronary plaque rupture and thrombosis (type 1). Although the use of the hs-troponin resulted in an increase in new prescriptions (anti-platelet, statin, and beta-blocker agents) and a 3-fold increase in coronary angiographies, this did not translate into a reduction of subsequent myocardial infarction/cardiovascular death during the

one year follow-up (20). In patients without chest pain or ischemic ECG changes hospitalized in cardiology and internal medicine departments, elevated troponin tests had no clinical utility and resulted in more downstream testing (21).

The current study in a real-life emergency department setting including a large proportion of patients with non-cardiac chest pain did not support these findings. Despite an increase in positive hs-troponin test results, the average number of diagnostic tests decreased in patients presenting to the ED with chest pain. This may indicate that physicians feel more confident about their own assessment when the test is negative but are also aware of the more sensitive nature of the test. A rapid myocardial infarction rule out protocol in chest pain of more than 6 hours and a negative hs-troponin test was found to have a high sensitivity and specificity (22). In the current study it is noteworthy that in 13% no troponin test was used to establish a non-cardiac chest pain diagnosis indicating that the clinical assessment remains an important factor in patients with chest pain.

Strengths and limitations

We used rigorous methods to extract data from health care records and assessed the extraction quality. Further, the data extraction over two years may allow to balance seasonal and other influencing factors. The following limitations warrant further discussion. We based the diagnosis on the discharge letters and follow-up records to the same hospital. Therefore, we were not able to assess all evaluations performed on an outpatient basis. However, the aim of this study was to assess the impact on the diagnostic evaluation in the ED. It can be assumed that only low risk patients were discharged for outpatient follow-up. Although we cannot rule out overdiagnosis of cardiovascular disease as we did not assess the correctness of the

diagnosis, the proportions of patients with cardiac illnesses were comparable to other studies (22).

Implications for research and clinical practice

Future studies should compare the judgment of clinicians combined with diagnostic tests to prediction rules for the diagnosis of cardiac chest pain. Overdiagnosis remains a matter of concern and diagnostic tests should be used in combination with clinical judgment. ED physicians may be at least equally accurate to rule in or out an acute coronary syndrome compared to a prediction rule developed in ED patients with chest pain (23). The current study indicates that the appropriate use of hs-troponin test may improve clinicians' confidence with their diagnosis in particular in patients with negative hs-troponin test results.

Conclusion

Although the introduction of the hs-troponin test resulted in a higher proportion of positive test results in patients with non-cardiac chest pain, we found a decrease in the average diagnostic tests performed in patients with chest pain presenting to an ED indicating an increased confidence of clinicians in their diagnosis.

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References

1. Bhuiya FA, Pitts SR, McCaig LF. Emergency department visits for chest pain and abdominal pain: United States, 1999-2008. NCHS Data Brief. 2010(43):1-8.

2. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr., et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130(25):e344-426.

3. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(3):267-315.

4. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 Appropriate Use Criteria for Coronary Revascularization in Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons. Journal of the American College of Cardiology. 2017;69(5):570-91.

5. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. The New England journal of medicine. 2000;342(16):1163-70.

6. Cayley WE, Jr. Diagnosing the cause of chest pain. Am Fam Physician. 2005;72(10):2012-21.

7. Buntinx F, Knockaert D, Bruyninckx R, De Blaey N, Aerts M, Knottnerus JA, et al. Chest pain in general practice or in the hospital emergency department: Is it the same? Fam Pract. 2001;18(6):586-9.

8. Blatchford O, Capewell S, Murray S, Blatchford M. Emergency medical admissions in Glasgow: General practices vary despite adjustment for age, sex, and deprivation. British Journal of General Practice. 1999;49(444):551-4.

9. Al-Saleh A, Alazzoni A, Al Shalash S, Ye C, Mbuagbaw L, Thabane L, et al. Performance of the high-sensitivity troponin assay in diagnosing acute myocardial infarction: systematic review and meta-analysis. CMAJ Open. 2014;2(3):E199-207.

10. Aldous SJ, Richards MA, Cullen L, Troughton R, Than M. A new improved accelerated diagnostic protocol safely identifies low-risk patients with chest pain in the emergency department. Acad Emerg Med. 2012;19(5):510-6.

11. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. The New England journal of medicine. 2009;361(9):858-67.

12. Bell KJL, Doust J, Glasziou P, Cullen L, Harris IA, Smith L, et al. Recognizing the Potential for Overdiagnosis: Are High-Sensitivity Cardiac Troponin Assays an Example? Ann Intern Med. 2019.

13. Wertli MM, Dangma TD, Muller SE, Gort LM, Klauser BS, Melzer L, et al. Non-cardiac chest pain patients in the emergency department: Do physicians have a plan how to diagnose and treat them? A retrospective study. PloS one. 2019;14(2):e0211615.

14. Burgstaller JM, Held U, Gravestock I, Klauser BS, Gort LM, Melzer L, et al. Introduction of the high-sensitive troponin in the emergency department: data and supplementary analyses, Data in Brief. 2019;in press.

15. Muller-Bardorff M, Hallermayer K, Schroder A, Ebert C, Borgya A, Gerhardt W, et al. Improved troponin T ELISA specific for cardiac troponin T isoform: assay development and analytical and clinical validation. Clin Chem. 1997;43(3):458-66.

16. Saenger AK, Beyrau R, Braun S, Cooray R, Dolci A, Freidank H, et al. Multicenter analytical evaluation of a high-sensitivity troponin T assay. Clin Chim Acta. 2011;412(9-10):748-54.

17. Zhelev Z, Hyde C, Youngman E, Rogers M, Fleming S, Slade T, et al. Diagnostic accuracy of single baseline measurement of Elecsys Troponin T high-sensitive assay for diagnosis of acute myocardial infarction in emergency department: systematic review and meta-analysis. Bmj. 2015;350:h15.

18. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Core Team.; 2019 [cited 2013. Available from: http://www.R-project.org/.

19. Mills NL, Churchhouse AM, Lee KK, Anand A, Gamble D, Shah AS, et al. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. Jama. 2011;305(12):1210-6.

20. Shah ASV, Anand A, Strachan FE, Ferry AV, Lee KK, Chapman AR, et al. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. Lancet (London, England). 2018;392(10151):919-28.

21. Shimoni Z, Arbuzov R, Froom P. Troponin Testing in Patients Without Chest Pain or Electrocardiographic Ischemic Changes. The American Journal of Medicine. 2017;130(10):1205-10.

22. Wildi K, Nelles B, Twerenbold R, Rubini Gimenez M, Reichlin T, Singeisen H, et al. Safety and efficacy of the 0 h/3 h protocol for rapid rule out of myocardial infarction. Am Heart J. 2016;181:16-25.

23. Visser A, Wolthuis A, Breedveld R, ter Avest E. HEART score and clinical gestalt have similar diagnostic accuracy for diagnosing ACS in an unselected population of patients with chest pain presenting in the ED. Emerg Med J. 2015;32(8):595-600.

Figure captions and legends

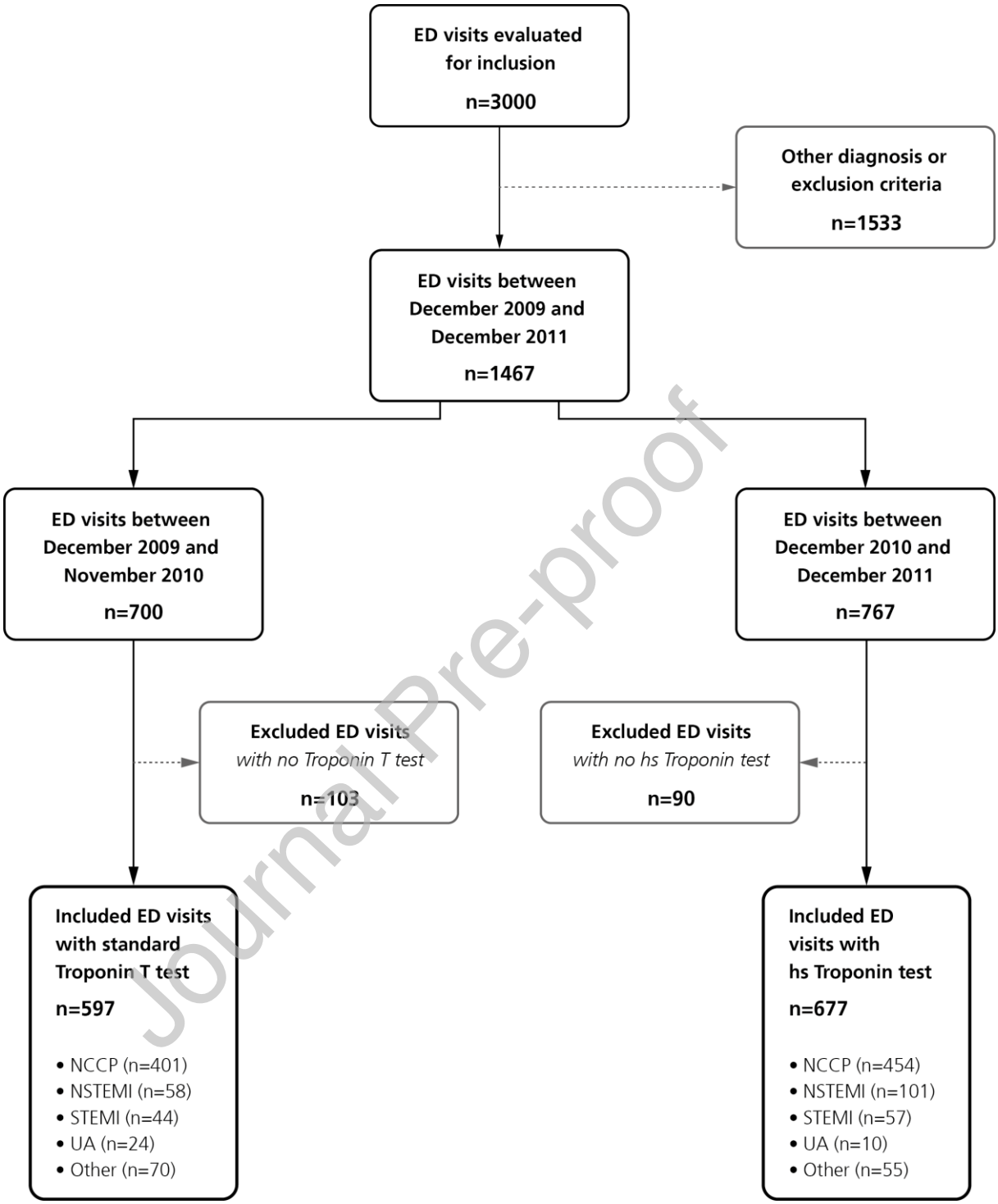

Figure 1.
Study flow

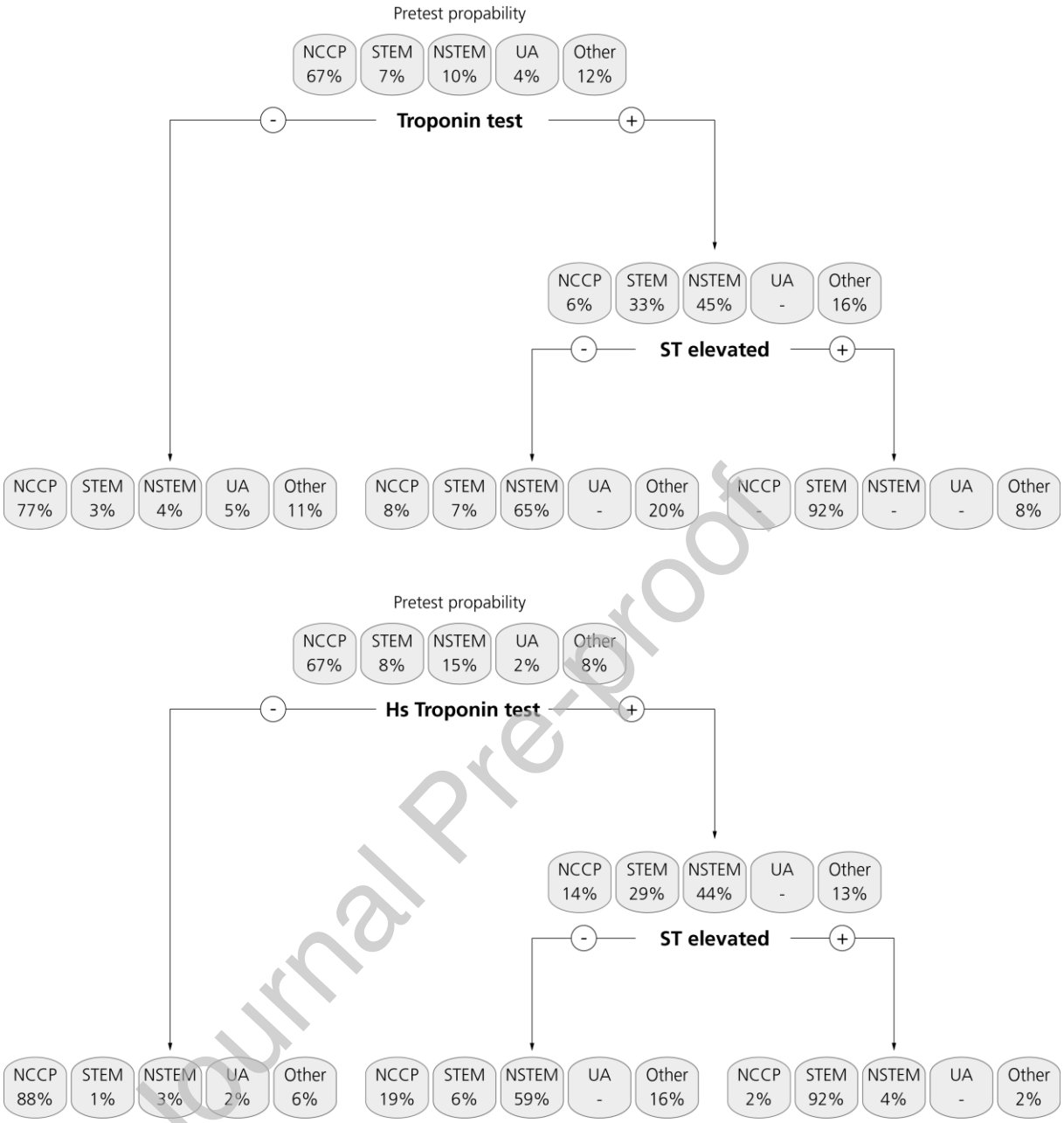

Figure 2.
Probabilities of having a non-cardiac and cardiac diagnosis
Panel A: standard troponin test period
Panel B: high-sensitive troponin test period

ST elevated, ST-elevation in the first ECG

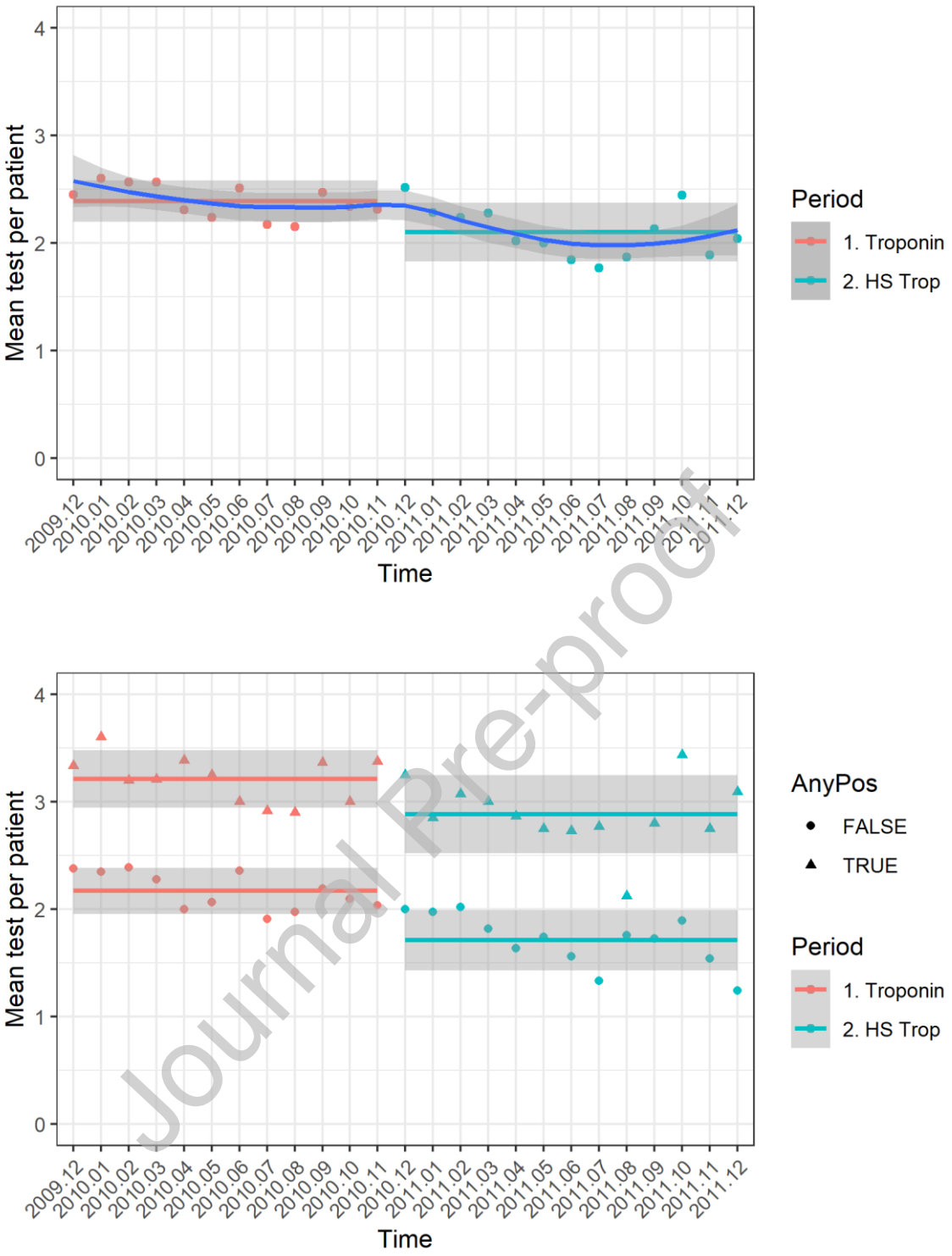

Figure 3.
Average monthly number of diagnostic tests per patients
Panel A: Overall average monthly tests per patient
Panel B: Average monthly test per patient with positive and negative troponin test

Table 1: Baseline characteristics of the study population (n= 1,274 patients)

Characteristics	Troponin	Hs-Troponin	p-value
	n (%) / mean (SD)		
n	597	677	
Age (mean (SD))	55.66 (17.30)	55.51 (16.91)	0.881
Gender (mean (SD))	370 (62.0)	420 (62.0)	1.000
BMI (mean (SD))	27.45 (4.73)	27.38 (4.86)	0.843
Profession			
Employee/white collar	91 (15.2)	197 (29.1)	<0.001
Blue collar	88 (14.7)	98 (14.5)	
Disabled	14 (2.3)	18 (2.7)	
Non-working	51 (8.5)	72 (10.6)	
Retired	195 (32.7)	232 (34.3)	
Unknown	158 (26.5)	60 (8.9)	
Civil status			
Divorced	75 (12.6)	86 (12.7)	0.150
No relationship	77 (12.9)	98 (14.5)	
Relationship	7 (1.2)	1 (0.1)	
Married	366 (61.3)	415 (61.3)	
Widowed	67 (11.2)	66 (9.7)	
Unknown	5 (0.8)	11 (1.6)	
Referral			
Self-referral	414 (69.3)	485 (71.6)	0.404
Physician referral	178 (29.8)	192 (28.4)	0.611
Additional by ambulance	144 (24.1)	171 (25.3)	0.894
Unknown	5 (0.8)	0 (0)	
Cardiovascular risk factors			
Smoking (%)			0.125
Still smoking	137 (22.9)	146 (21.6)	
Stopped	99 (16.6)	147 (21.7)	
Never	147 (24.6)	165 (24.4)	
Unknown	214 (35.8)	219 (32.3)	
Family history for MI	132 (22.1)	166 (24.5)	0.318
Unknown	239 (40.0)	281 (41.5)	
Cocaine use	5 (0.8)	6 (0.9)	0.980
Unknown	519 (86.9)	586 (86.6)	
Preexisting diseases			
Diabetes	72 (12.1)	76 (11.2)	<0.001
Diet	16 (2.7)	11 (1.6)	0.539
OAD	41 (6.9)	51 (7.5)	
Insulin	15 (2.5)	14 (2.1)	

Unknown	46 (7.7)	9 (1.3)	
PAD			<0.001
Yes	20 (3.4)	15 (2.2)	
Unknown	107 (17.9)	40 (5.9)	
Stroke			0.001
Yes	24 (4.0)	20 (3.0)	
Unknown	67 (11.2)	39 (5.8)	
MI			<0.001
Yes	98 (16.4)	96 (14.2)	
Unknown	61 (10.2)	23 (3.4)	
Psychiatric disease	86 (14.4)	81 (12.0)	<0.001
Unknown	85 (14.2)	52 (7.7)	
Cardiovascular disease	328 (54.9)	329 (48.6)	0.012
Unknown	52 (8.7)	47 (6.9)	
Gastrointestinal disease	85 (14.2)	87 (12.9)	0.060
Unknown	75 (12.6)	60 (8.9)	
Cancer disease	25 (4.2)	22 (3.2)	0.020
Unknown	78 (13.1)	58 (8.6)	
Thyroid disease	26 (4.4)	34 (5.0)	0.025
Unknown	78 (13.1)	57 (8.4)	
Lung disease	45 (7.5)	37 (5.5)	0.015
Unknown	75 (12.6)	58 (8.6)	
Gyn-/urologic disease	64 (10.7)	60 (8.9)	0.012
Unknown	77 (12.9)	57 (8.4)	
Rheumatoid disease	27 (4.5)	17 (2.5)	0.002
Unknown	80 (13.4)	58 (8.6)	
Medications			
Acetylsalicylic acid	177 (29.6)	184 (27.2)	0.350
Unknown	13 (2.2)	22 (3.2)	
Statin	144 (24.1)	140 (20.7)	0.106
Unknown	12 (2.0)	24 (3.5)	
Antihypertensive therapy	257 (43.0)	290 (42.8)	0.534
Unknown	14 (2.3)	23 (3.4)	
PPI	101 (16.9)	111 (16.4)	0.529
Unknown	14 (2.3)	23 (3.4)	
Analgesic use	90 (15.1)	95 (14.0)	0.561
Unknown	14 (2.3)	22 (3.2)	
Antipsychotic use	91 (15.2)	100 (14.8)	0.642
Unknown	15 (2.5)	23 (3.4)	

BMI, body mass index; PAD, peripheral arterial disease; MI, myocardial infarction; CVD, cardiovascular disease; MI, myocardial infarction; GI, gastrointestinal; PPI, proton pump inhibitor; OAD, oral antidiabetic drugs

Table 2: Diagnosis in the standard troponin test and the hs-troponin test period

	NCCP	STEMI	NSTEMI	UA	Other
Troponin test period			*N (%)*		
Patients	401 (67.2)	44 (7.4)	58 (9.7)	24 (4.0)	70 (11.7)
Any positive trop test	8 (2.0)	43 (97.7)	51 (87.9)	0 (0.0)	20 (28.6)
Trop Test 1 +	6 (1.5)	28 (63.6)	38 (65.5)	0 (0.0)	12 (17.1)
Trop Test 2 or 3 +	2 (0.5)	15 (34.1)	13 (22.4)	0 (0.0)	8 (11.5)
Hs-troponin test period					
Patients	454 (67.1)	57 (8.4)	101 (14.9)	10 (1.5)	55 (8.1)
Any pos hs-trop test	28 (6.1)	57 (100)	98 (97.0)	0 (0.0	27 (49.1)
Trop Test 1 +	22 (4.8)	57 (100)	83 (82.2)	0 (0.0)	23 (41.8)
Trop Test 2 or 3 +	6 (1.3)	0 (0)	15 (14.8)	0 (0.0)	4 (7.3)

NCCP, non-cardiac chest pain; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; UA, unstable angina; Hs, high-sensitive; Trop, troponin; +, positive test result

Table 3: Diagnostic tests performed in the standard troponin and in the hs troponin test period

	NCCP	STEMI	NSTEMI	UA	Other
Standard troponin			*N (%)*		
Patients	401 (67.2)	44 (7.4)	58 (9.7)	24 (4.0)	70 (11.7)
ECG	390 (97%)	41 (93%)	57 (98%)	24 (100%)	67 (96%)
Coronary angiography	23 (5.7%)	35 (80%)	48 (83%)	13 (54%)	42 (60%)
Echocardiography	32 (8%)	24 (55%)	16 (28%)	6 (25%)	26 (37%)
Mibi Scintigraphy	5 (1.2%)	0 (0%)	2 (3.4%)	0 (0%)	6 (8.6%)
Treadmill test	19 (4.7%)	0 (0%)	2 (3.4%)	2 (8.3%)	6 (8.6%)
Computer tomography	39 (9.7%)	0 (0%)	1 (1.7%)	1 (4.2%)	6 (8.6%)
Chest X-ray	269 (67%)	35 (80%)	52 (90%)	20 (83%)	61 (87%)
Sonography abdomen	20 (5%)	0 (0%)	1 (1.7%)	1 (4.2%)	3 (4.3%)
Gastroscopy	6 (1.5%)	1 (2.3%)	0 (0%)	3 (12%)	4 (5.7%)
Pleura sonography	1 (0.25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lung function test	2 (0.5%)	0 (0%)	1 (1.7%)	2 (8.3%)	4 (5.7%)
Hs-troponin	454 (67.1)	57 (8.4)	101 (14.9)	10 (1.5)	55 (8.1)
ECG	452 (100%)	51 (89%)	99 (98%)	9 (90%)	54 (98%)
Coronary Angiography	14 (3.1%)	52 (91%)	79 (78%)	4 (40%)	27 (49%)
Echocardiography	26 (5.7%)	22 (39%)	25 (25%)	2 (20%)	19 (35%)
Mibi Scintigraphy	4 (0.88%)	2 (3.5%)	0 (0%)	1 (10%)	1 (1.8%)
Treadmill test	14 (3.1%)	1 (1.8%)	3 (3%)	0 (0%)	3 (5.5%)
Computer tomography	32 (7%)	2 (3.5%)	3 (3%)	0 (0%)	5 (9.1%)
Chest X-ray	222 (49%)	39 (68%)	81 (80%)	5 (50%)	36 (65%)
Sonography abdomen	12 (2.6%)	1 (1.8%)	2 (2%)	0 (0%)	1 (1.8%)
Gastroscopy	4 (0.88%)	2 (3.5%)	3 (3%)	0 (0%)	0 (0%)
Pleura sonography	1 (0.22%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lung function test	4 (0.88%)	0 (0%)	6 (5.9%)	0 (0%)	1 (1.8%)

NCCP, non-cardiac chest pain; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; UA, unstable angina; ECG, electrocardiogram